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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,164	METCALF, BENJAMIN J.	
	Examiner Patricia A. Duffy	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 25 July 2005 and 19 December 2005.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-8 and 18-22 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-8 and 18-22 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on 7-25-05 and 12-19-2005 have been entered. The amendment to the claims filed 4-10-07 have been entered into the record.

Claims 1-8 and 18-22 are pending and under examination.

Rejections Withdrawn

The rejection of claims 1, 2 and 8 under 35 USC 102(b) as being anticipated by Anilionis et al (WO 90/02557, published March 22, 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) is withdrawn in view of the amendment to the claims.

The rejection of claims 3-5 under 35 USC 103(a) as being unpatentable over Anilionis et al (WO 90/02557, published March 22, 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims 1, 2, and 8 above and in view of Guzman et al (Journal of Bacteriology, 177(14):4121-4130, 1995) is withdrawn in favor of the new grounds of rejection set forth below.

The rejection of claims 3 and 6 under 35 USC 103(a) as being unpatentable over Anilionis et al (WO 90/02557, published March 22, 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims 1, 2, and 8 above and in view of Mertens et al (Gene, 164:9-15, 1995) is withdrawn in favor of the new grounds of rejection set forth below.

The rejection of claims 3, 6 and 7 under 35 USC 103(a) as being unpatentable over Anilionis et al (WO 90/02557, published March 22, 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims 1, 2, and 8 above and in view of Mertens et al (Gene, 164:9-15, 1995) and Novagen Inc, (admittedly commercially available in specification page 15, line 34) is withdrawn in favor of the new grounds of rejection set forth below.

Rejections Maintained

Claims 1-8 and 18-22 are rejected under 35 USC 112, second paragraph as being indefinite for failing to particular point out and distinctly claim the subject matter which applicant regards as the invention for reasons made of record.

Applicant's arguments have been carefully considered but are not persuasive. Applicant's claims are directed broadly to "tightly regulated" and specifically to T7 and arabinose inducible promoters. It is noted that tightly regulated promoters also "leak". For example, Baneyx (Current Opinion in Biotechnology, 10:411-421, 1999) teach that plasmid-encoded T7 promoters are leaky (see page 413, column 1, first paragraph). Therefore, Applicants amendment would necessarily exclude T7 promoters, because they are "leaky", although at a minimal level. Applicant's declaration has been carefully considered. Applicant demonstrates that the arabinose promoter, while tightly regulated is has a "minimal level of leak" as is consistent with the art teachings and is substantially less than the leak of the lac promoter in a side by side comparison. This is not persuasive because the claims are not commensurate with the declaration. These teachings establish again that there are degrees of "leak", even with a tightly regulated promoter. The art acknowledges and Declarant confirms that tightly regulated promoters have a minimal level of "leak", and they can and do leak. Therefore, leaky is a also term of degree, the requisite basis for comparison is not set forth in the claims and the claims are not

commensurate with the declaration.. It is strongly suggested that Applicants consider amending the claim to recite the specific basis for comparison that is set forth in the specification and the declaration. The skilled artisan would be unable to ascertain what degree of "leaky regulated" is the basis for comparison, because even tightly regulated promoters have a minimal level of "leak" and therefore "leaky regulated" includes the T7 and arabinose promoters of the invention.

New Rejections Based on Amendment

Claims 1-8 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims now recite "...when the recombinant PAL [P6] is under the control of a "leaky regulated promoter". The specification discusses promoters that are not under "tight transcriptional regulation" at page 3, lines 29-35. The specification also theorized that "somewhat leaky transcription" contributed to low levels of transcription of lapidated P6 protein. The concepts of not under tight transcriptional regulation is not synonymous with "leaky regulated promoter", because even tightly transcriptional regulation can have some "leak". The specification does not discuss the ability of the promoters to be regulated or not. Therefore, the newly created subgenus of "leaky regulated promoters" changes the scope of the disclosure and is therefore new matter. The specification does not discuss the levels of "regulation" with respect to the "leak".

Claims 1-5, 8, 18, 19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anilines et al (WO 90/02557, published 22 March 1990) in view of Nelson et al (Infection and Immunity, 56(1):128-134, 1988), Guzman et al (Journal of

Bacteriology, 177(14):4121-4130, 1995) and Makrides et al (Microbiological Reveiws, 60(3):512-538, Sept 1996).

Anilines et al teach a plasmid containing an outer membrane protein of *Haemophilus influenzae* encoding a protein having 153 amino acids and an approximate molecular weight of 16,000 daltons which they call PBOMP-1 (see page 1, first full paragraph). The PBOMP-1 of Anilines et al is "P6" in veiw of Nelson et al that teaches that "P6" is *Haemophilus influenzae* protein having 153 amino acids and a calculated molecular weight of 16,089 daltons (page 131, column 2, second paragraph). The plasmid of Anilines et al is designated pPX166 and expresses PBOMP-1 under regulation of the lac promoter in *Escherichia coli* JM1003 (page 81, lines 3-22). Anilines et al teach that PBOMP-1 as expressed by recombinant *E. coli* are lipoproteins (see page 71, lines 30-33). The plasmid of Anilines et al was transformed into and expressed in several *E. coli* strains including JM103 and HB101 (see page 81, lines 23-25). Anilines et al differs by not teaching a plasmid with PBOMP-1 and a "tightly regulated promoter" such as the arabinose inducible promoter or a T7 promoter. However, Anilines et al specifically teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and hence, expression of the gene and depending upon the host cell system utilized any number of suitable promoters may be used (page 29, lines 10-15).

Guzman et al (Journal of Bacteriology, 177(14):4121-4130, 1995) teach vectors for use in *E. coli* that are both positively and negatively modulated, have a high level of expression and comprise the arabinose PBAD promoter and are not expressed in the absence of the inducer arabinose. Guzman et al teach the vector pBAD18-cm (see Figure 1A, page 4122). pBAD18-cm is the same vector utilized in the instant application to express the P6 protein (page 16, line 17-24) from claimed plasmid pPX4020.

Makrides et al teach the art recognized strategies for achieving high-level expression of genes in *E. coli*. Makrides et al teach that promoters for use in *E. coli* (Table 1, page 514) should have certain characteristics to render it suitable for high-level protein synthesis. First, it must be strong, resulting in the accumulation of protein making upto 10 to 30% of the total cellular protein. Second, it should exhibit a minimal level of basal transcription (i.e. not leaky). Large-scale gene expression preferably employs cell growth to a high density and minimal promoter activity, followed by induction or derepression of the promoter. Tight regulation of a promoter is essential for the synthesis of proteins that may be detrimental to the host cell. The third important characteristic for high expression is its inducibility in a simple cost effective manner (see page 513, column 1 to page 514, column 2). Makrides et al teach at Table 1 page 514, that araBAD and T7 are promoters used for the high-level expression of genes in *E. coli*.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to subclone the PBOMP-1 (i.e. innately the P6 protein as evidenced by Nelson et al) of Anilines et al into any of the arabinose inducible vectors of Guzman et al including pBAD18-cm because Anilines et al teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, Makrides et al teach that it is desirable to use strong, tightly-regulated inducible promoters in order to obtain a high level of transcription and the vectors of Guzman et al meet these criteria. In the absence of any factual evidence demonstrating a protein or nucleic acid sequence difference between the nucleic acids encoding the P6 *Haemophilus influenzae* proteins of the prior art and the nucleic acid encoding the P6 *Haemophilus influenzae* protein of plasmid pPX4020, the subcloning of a known protein into a different expression vector is highly conventional and routine in the art. Further, should a sequence difference be factually demonstrated in response to this office action, then Applicants are officially on notice that the claimed plasmid would necessarily be subject to a deposit.

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requirement pursuant to 112, first paragraph. One skilled in the art would expect the subcloning from lac into vectors demonstrating the criteria of Makrides et al would provide for increased expression of the target protein.

Claims 1-3, 6, 8, 18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anilines et al (WO 90/02557, published 22 March 1990) in view of Nelson et al (Infection and Immunity, 56(1):128-134, 1988), Mertens et al (Gene, 164:9-15, 1995) and Makrides et al (Microbiological Reveiws, 60(3):512-538, Sept 1996).

Anilines et al teach a plasmid containing an outer membrane protein of *Haemophilus influenzae* encoding a protein having 153 amino acids and an approximate molecular weight of 16,000 daltons which they call PBOMP-1 (see page 1, first full paragraph). The PBOMP-1 of Anilines et al is "P6" in view of of Nelson et al that teaches that "P6" is *Haemophilus influenzae* protein having 153 amino acids and a calculated molecular weight of 16,089 daltons (page 131, column 2, second paragraph). The plasmid of Anilines et al is designated pPX166 and expresses PBOMP-1 under regulation of the lac promoter in *Escherichia coli* JM1003 (page 81, lines 3-22). Anilines et al teach that PBOMP-1 as expressed by recombinant *E. coli* are lipoproteins (see page 71, lines 30-33). The plasmid of Anilines et al was transformed into and expressed in several *E. coli* strains including JM103 and HB101 (see page 81, lines 23-25). Anilines et al differs by not teaching a plasmid with PBOMP-1 and a "tightly regulated promoter" such as the arabinose inducible promoter or a T7 promoter. However, Anilines et al specifically teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and hence, expression of the gene and depending upon the host cell system utilized any number of suitable promoters may be used (page 29, lines 10-15).

Mertens et al (Gene, 164:9-15, 1995) teach vectors for use in *E. coli* that are provide for high-level of expression. The plasmid comprises the PT7 promoter. Mertens et al teach that the decision as to which promoter to use can be based on various criteria, such a promoter strength and control, economy, ease of utilization or the conditions under which the promoter is to be used (e.g. temperature condition and choice of host strains or medium; page 9, column 2-page 10, column 1). Mertens et al teach that lambda PI and PT7 are among the strongest promoters known in *E. coli*, then can be tightly regulated and allow a free choice of host strains or induction conditions. Mertens et al teach that the described vectors have the potential to considerably improve the expression level of other heterologous genes (page 14, column 1, last full paragraph).

Makrides et al teach the art recognized strategies for achieving high-level expression of genes in *E. coli*. Makrides et al teach that promoters for use in *E. coli* (Table 1, page 514) should have certain characteristics to render it suitable for high-level protein synthesis. First, it must be strong, resulting in the accumulation of protein making upto 10 to 30% of the total cellular protein. Second, it should exhibit a minimal level of basal transcription (i.e. not leaky). Large-scale gene expression preferably employs cell growth to a high denisity and minimal promoter activity, followed by induction or derepression of the promoter. Tight regulation of a promoter is essential for the synthesis of proteins that may be detrimental to the hot cell. The third important characteristic for high expression is its inducibility is a simple cost effective manner (see page 513, column 1 to page 514, column 2). Makrides et al teach at Table 1 page 514, that araBAD and T7 are promoters used for the high-level expression of genes in *E. coli*.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to subclone the PBOMP-1 (i.e. innately the P6 protein as evidenced by Nelson et al) of Anilines et al into any of the pT7 containing vectors of Mertens et al because Anilines et al teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced

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(page 29, lines 27-30) and for purposes of expressing a cloned gene, Makrides et al teach that it is desirable to use strong, tightly-regulated, inducible promoters in order to obtain a high level of transcription and the vectors of Mertens et al meet these criteria and Mertens et al teach that the PT7 containing vectors have the potential to considerably improve the expression level of other heterologous genes. One skilled in the art would expect the subcloning from lac into vectors demonstrating the criteria of Makrides et al would provide for increased expression of the target protein.

Claims 7 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anilines et al (WO 90/02557, published 22 March 1990), Nelson et al (Infection and Immunity, 56(1):128-134, 1988), Mertens et al (Gene, 164:9-15, 1995) and Makrides et al (Microbiological Reveiws, 60(3):512-538, Sept 1996) as combined *supra* for claims 1-3, 6, 8, 18 and 21 and further in view of Novagen Inc., admittedly commercially available in specification page 15, line 34).

The teachings of Anilines et al (WO 90/02557, published 22 March 1990), Nelson et al (Infection and Immunity, 56(1):128-134, 1988), Mertens et al (Gene, 164:9-15, 1995) and Makrides et al (Microbiological Reveiws, 60(3):512-538, Sept 1996) are set forth *supra*. The teachings as combined differ by not teaching the pET-27b Novagen plasmid used for expression of the P6 protein.

Novagen Inc. teaches a commercially available vector pET-27b. This commercially available expression vector for *E. coli* and that the commercially available vector is the specific vector comprising the T7 promoter that was used in the instant specification in the construction of the claimed pPX4019 plasmid (specification page 15, line 34).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to subclone the PBOMP-1 (i.e. innately the P6 protein as evidenced by Nelson et al) from the vector as combines *supra* into the commercially available vector pET-27B of Novagen et al because Anilines et al teach that for purposes

of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription or purposes of expressing a cloned gene, Makrides et al teach that is desirable to use strong, tightly-regulated, inducible promoters in order to obtain a high level of transcription, Mertens et al teach that the PT7 is among the strongest promoters known in *E. coli*, can be tightly regulated and provide a free choice of host strains or induction conditions. One would have been motivated to use commercially available expression vectors to reduce the work in preparing a vector from scratch in the laboratory. In the absence of any factual evidence demonstrating a protein or nucleic acid sequence difference between the nucleic acids encoding the P6 *Haemophilus influenzae* proteins of the prior art and the nucleic acid encoding the P6 *Haemophilus influenzae* protein of plasmid pPX4019, the subcloning of a known protein into a different expression vector is highly conventional and routine in the art. Further, should a sequence difference be factually demonstrated in response to this office action, then Applicants are officially on notice that the claimed plasmid would necessarily be subject to a deposit requirement pursuant to 112, first paragraph. One skilled in the art would expect the subcloning from one T7 vector into another T7 expression vector demonstrating the criteria of Makrides et al would provide for increased expression of the target protein.

Response to Arguments

Applicants argue that their results are unexpected and long felt need in the art, however the art teaches that the vectors employed in the specification were known by the art to provide for high-level expression of genes in *E. coli*. The long felt need argument is not persuasive, because the art pursued recombinant P6 production absent lipidation and that production of P6 was successful for vaccine production in the art. Therefore, the art is not seen to have a long felt need for the lipidated form, when the non-lipidated form was successfully produced as a vaccine component. With regard to the allegation of unexpected results, it is noted that evidence asserted to establish unobvious results,

applicant has a burden of indicating how the examples representing the claimed invention relate to the prior art examples and how the latter represent the closest prior art, submitting evidence reasonably commensurate in scope with the claimed subject matter, establishing that the differences are in fact unexpected and unobvious and of statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318 (BPAI 1992). In the instant case, the tightly regulated promoters T7 and arabinose were recognized by the art to provide for high-level expression in *E. coli*. The art taught these promoters were desirable and that they would be reasonably expected to achieve high levels of expression. The statute does not require absolute 100% guaranteed success.

Applicant argues that there is no suggestion in the art to use tightly regulated promoters and no reasonable expectation of success because "potential use" is not a reasonable expectation. "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). In the instant case, the promoter of the art as combined were well established in the art for achieving high level of expression of heterologous genes in *E. coli*. The art specifically guides the skilled artisan to these promoters for high levels of expression in *E. coli*. It is not an invitation to experiment, the promoters were known to be successful as they form the basis of commercially available expression plasmids which applicants used to product the lapidated P6 protein. Applicants argue that laboratories had tried and failed to produce usable quantities of P6 and it was Applicants who figured out how to produce such. This is not persuasive because the claims are not drawn to a method and the art had produced

lipidated P6, albeit in smaller quantities. In order to increase the quantity, the art would have looked to those promoters that were known provide the requisite properties. The claims are drawn to plasmids and host cells. Expression of the lipidated form is a property of the host cell because it is the host cell that possesses the machinery that produces the lipidation. The plasmid merely encodes the protein with the appropriate signal sequence, if the host cell does not provide the machinery the protein will not be lipidated, despite having the argued signal sequence and processing site. Applicant's comments on this are simply not true, the host cell provides lipidation not the plasmid as recited in the claims. Given the teachings as combined the plasmid and host cells are obvious.

Status of Claims

Claims 1-8 and 18-22 stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Jeffrey Siew can be reached on 571-272-0787.

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The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy
Patricia A. Duffy

Primary Examiner

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